

REMARKS

Claims 1-38 are pending in the instant application, and all of the pending claims are rejected.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejects claims 1-24 and 28-38 because the claim language encompasses cross-species transfer. Applicants previously changed the claim language to recite "mammalian" cells and animals produced therefrom as are the cells specifically exemplified in the specification.

The Examiner acknowledges that the following types of claims are enabled and therefore patentable under 35 U.S.C. 112, first paragraph:

1. Method of preparing a reconstructed nonprimate mammalian oocyte;
2. Method of reconstituting a nonprimate mammalian embryo;
3. Method of producing a transgenic nonprimate mammalian embryo;

and

4. Method of cloning a nonprimate mammal

where the donor cell, the oocyte and the surrogate mother are of the same species.

The Examiner references two literature articles for the proposition that cloning primates was unpredictable, especially when somatic cells were used instead of embryonic cells.

Purely in the interest of advancing prosecution and securing rapid allowance of a patent, Applicants herein change the claim language to the types of claims mentioned as patentable by the Examiner as set forth, *supra*. Applicants explicitly make of record that this change to the claim language is no manner an acquiescence as to the merits of the Examiner's position. Applicants respectfully

remind the Examiner that the law does not require absolute predictability or certainty to fulfill the requirements of the patent statute as regards enablement. In fact, the courts have specifically stated that a great deal of experimentation is acceptable before the threshold to undue experimentation is passed thereby leading to a finding a non-enablement. See, e.g. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1998). As is the case with the instant invention, one of ordinary skill in the art could use the teachings of this specification to reproduce successfully cloned organisms without undue experimentation. It would simply be a matter of routine screening at every step to determine whether the nuclear transfer was successful and whether the embryo, fetus and animal was growing and developing. Such routine screening has been found to provide an enabling disclosure. Applicants explicitly reserve the right to pursue claims at least as broad as those presently amended in additional United States patent applications.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner indicates that claims 1-18 and 20-38 are indefinite and unclear for the following reasons:

1. There is no antecedent basis for “the method” in the phrase “obtained according to the method” as recited in claims 25-27 (Should change to “a method”);
2. Claim 27 recites “non-human” in the preamble and “mammalian” in the method steps (Should change to “non-human mammalian” in both claims 25 and 27);
3. Claims 1, 10, 20 and 25-28 recite “recently expelled” (Should delete “recently”).

Applicants herein make the noted minor changes in order to provide proper antecedent basis or to remove the unclear adverb “recently.”

Rejection under 35 U.S.C. §102(b)

The Examiner rejects all of claims 1-28 as anticipated by one or more of the following prior art references.

1. Schnieke et al., Science 278:2130-2133 (1997)

The Examiner rejects claims 25-27 as anticipated by Schnieke *et al.* According to the Examiner, Schnieke *et al.* teach sheep embryos, sheep fetuses and live born sheep from transgenic methods. The Examiner indicates that Applicants must distinguish the prior art animals from those presently claimed.

Applicants herein clearly distinguish the prior art animals from those presently claimed. Applicants submit that there are major differences between the method taught by Schnieke *et al.* and the method recited in claim 25. An embryo obtained by the present method provides a higher yield of development and birth of cloned animals than an embryo obtained by the methods taught by Schnieke *et al.* The Examiner is directed to Table 1 of Schnieke *et al.* where it is presented that 3.4% of embryos produced with memory epithelium cells gave birth to an offspring, and 5.8% and 7.7% of fetal fibroblasts gave birth to an offspring. Quite to the contrary, the present invention provides far superior and unexpected results. Applicants respectfully direct the Examiner's attention to the Declaration of Lawrence D. Smith pursuant to 37 C.F.R. 1.132, submitted herewith as Exhibit A. There Declarant states under oath that 40% of embryos gave birth to offspring when nuclear transfer occurred in a telophase II oocyte according to the instant invention. In view of this astonishing and unexpected result, it is clear that the embryos produced according to the method of the present invention are of higher quality than those produced by the method described by Schnieke *et al.*

2. Echelhard, U.S. Patent 6,580,017 B1

The Examiner rejects claims 1-38 as anticipated by Echelhard. The Examiner contends that Echelhard teaches methods for producing reconstructed

goat oocytes, reconstituted goat embryos, methods for producing transgenic goat embryos, and methods of cloning a goat comprising incubating goat oocytes in telophase II and then further incubating the oocyte in the presence of cytochalasin B, enucleating the activated, telophase II oocyte by aspiration, transferring a cultured goat fetal fibroblast which contains a DNA sequence encoding antithrombin III into the perivitelline space of the enucleated oocyte, fusing the reconstructed oocyte by electrofusion, and culturing the reconstituted oocyte to produce a transgenic embryo which is then transferred to a surrogate mother. The Examiner maintains that the fibroblast donor cells were inherently in one of G0, G1, S, G2 or M stages.

Applicants previously explained that Echelhard teaches using ethanol for treating oocytes and that this provides negative results when cloning the fibroblast cells. Applicants indicated that the results presented in Table 2 of Echelhard demonstrate that oocytes treated with ethanol in telophase failed to give valuable embryos and fetuses after transfer and that no embryos, fetus or offspring were found still living or in development. Moreover, Applicants indicated that no pregnancies were observed with embryos generated by the ethanol enucleation/activation protocol. Hence, Applicants explained that the procedure of Echelhard does not work and is not operable. Even further, Applicants explained that Echelhard does not teach or suggest enucleation of activated oocytes performed precisely when undergoing expulsion of a second polar body or after the activated oocyte has expelled the second polar body. Such is the case with the methods of the present invention.

The Examiner replies that while the ethanol treated oocytes of the specific example did not yield live born goats, there is no evidence that if mature oocytes were activated at MII with ethanol that live births would not occur. The Examiner says that the present specification supports that theory. Moreover, the Examiner contends that the oocytes of Echelhard are inherently activated since they are in telophase. The Examiner cites to column 14, lines 32-35 as evidence that Echelhard teaches enucleation precisely when the oocyte is undergoing expulsion of the second polar body. Further, the Examiner cites to column 19, lines 21-25

as evidence that Echelhard teaches enucleation of telophase II oocytes by aspirating the extruded second polar body.

Applicants respectfully submit that Echelhard is not prior art to the present invention. Applicants submit herewith a Declaration of Lawrence C. Smith pursuant to 37 C.F.R. 1.131 (Exhibit B). Therein, Dr. Smith states under oath that the cloning method that is the subject of the present application was conceived before November of 1998. Moreover, Dr. Smith provides a copy of a research grant proposal dated November 28, 1997 wherein a description of the method presently claimed is provided (See, e.g. pages 7 to 10). Clearly, Applicants conceived of the present invention and were diligent in reducing it to practice long before the effective filing date of Echelhard, namely November 2, 1998. Applicants constructively reduced the invention to practice on April 28, 1999 with the filing of U.S. Provisional Application No. 60/131,469, and Applicants actually reduced the invention to practice prior to that date.

Rejection under 35 U.S.C. §103

Bordignon et al., Molec. Reprod. Devel. 49, 29-36 in view of Schnieke et al.,
Science 278:2130-2133 (1997)

The Examiner rejects claims 1-24 and 28-38 over Bordignon *et al.* in view of Schnieke *et al.* The Examiner maintains that Bordignon *et al.* suggest or motivates one of skill in the art to try using enucleated telophase oocytes by stating that the telophase approach reduces the amount of ooplasm that needs to be removed in the enucleation procedure (citing page 34, column 2, paragraph 2, line 13 to page 35, column 1, line 1) and that UV irradiation and Hoechst 33342 staining are not needed (citing page 35, column 1, lines 1-4), both of which are associated with developmental deficiencies (citing page 35, column 1, lines 4-8). Moreover, the Examiner cites Borgignon *et al.* as teaching that oocyte activation can readily be determined by observing an extruding second polar body (citing page 35, column 1, lines 12-15).

The Examiner maintains that Schnieke *et al.* suggest or motivates one of skill in the art to try using enucleated telophase oocytes by stating that transgenesis by nuclear transfer is more efficient because transfected cells can be analyzed prior to nuclear transfer, the problem of delayed integration of the transgene into the embryonic genome is obviated, and the sex of the transgenic animal can be determined (citing page 2133, column 1, lines 3-5; paragraph 2; and paragraph 3, lines 1-6).

Applicants previously explained that Bordignon *et al.* teach a telophase enucleation technique to produce cloned animals from early embryonic blastomeres. ***Bordignon et al. do not teach or suggest cloning of animals using cells other than early embryonic blastomeres.*** Moreover, it was of general belief in the art (as mentioned on page 5, lines 1 to 5 of the instant specification) that an oocyte could not be activated before enucleation and receive nuclei from cultured cells of embryonic, germinal and somatic origin.

The Examiner says these arguments are not convincing for the following reasons:

1. The present specification cites two references that taught enucleation prior to activation (citing page 5, lines 1-5);
2. There is no evidence that the art as a whole believed that activation could not occur prior to enucleation;
3. Bordignon *et al.* allegedly teach activating an oocyte prior to enucleation and enucleating an oocyte that has expelled a second polar body; and
4. There is no evidence that the enucleated telophase oocyte of Bordignon *et al.* would not yield a live-born nonhuman mammal.

Respectfully, the Examiner has not set forth a proper *prima facie* case of obviousness. The references when combined simply do not reach the present invention as claimed. One of ordinary skill in the art simply would not arrive at the presently claimed subject matter by combining a solution for insuring the integration of a transgene to an embryo as described by Schnieke *et al.* with a

method for reconstituting oocytes and cloned bovine embryo using a blastomere as a nuclei donor.

Applicants submit that *Bordignon et al. teach cloning blastomeres*. *Blastomeres are totally different from a germinal or somatic nucleus or cell* both biochemically and in differentiation state. This is evident from the fact that germinal and somatic cells have to be reprogrammed as Applicants have previously explained. This is a realization that could not be deduced by one of ordinary skill in the art prior to the instant invention. As the Examiner states, Schnieke *et al.* teach producing transgenic sheep by genetically transformed fibroblasts that are actively dividing at the moment of transfer in the recipient oocyte. Applicants agree with the Examiner that this way of selecting transgenic embryos having a transgene genomically integrated offers an advantage. However, a technical approach as taught by Schnieke *et al.* is not relevant in view of a new mammalian cloning method for improving the cloning yield in a non-primate mammal.

Regarding the position that activation of an oocyte before nucleation is not obvious from the prior art, Applicants reiterate that Bordignon *et al.* teach a cloning method using blastomeres. These are cells completely different from germinal and somatic cells according to the instant invention. Applicants agree with the Examiner to the extent that from the teachings of Bordignon *et al.* there is no explicit evidence that an enucleated telophase oocyte in which a nucleus from a blastomer is transferred would not reasonably be expected to yield a live born non-human mammal when a transfected cell is used as a nuclear donor. Nevertheless, this affirmation is contrary to the approach of Schnieke *et al.* in which transgenic transfection, long-lasting culture and selection of transgene expressing cells prior to transfer into a recipient oocyte must be performed before cloning. Also, there is no explicit evidence that an enucleated telophase oocyte into which a blastomer nucleus has been transferred as taught by Bordignon *et al.* would be expected to yield a live born non-human mammal.

Fees

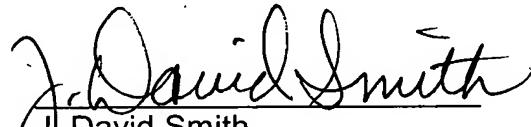
No additional fees are believed to be necessitated by the instant Response. However, should this understanding be erroneous, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing Amendments and Remarks into the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited. Should a discussion be helpful in resolving any outstanding issues, the Examiner is invited to telephone the undersigned at (201) 487-5800.

Respectfully submitted,

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